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A Retrospective Look at Recent COVID-19 Articles Published in Cell Transplantation: Research Leading to Further Understanding

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Abstract

During the past 18 months as the world dealt with the COVID-19 pandemic, articles published in *Cell Transplantation* (*CT*) voiced unique perspectives on the disease which have since been supported by additional research. Intrigued by the variability in COVID-19 severity, *CT* authors explored the influence of variants in angiotensin-converting enzyme 2 (ACE2) and the transmembrane serine protease 2 (TMPRSS2) genes, as well as the role of androgen receptors on disease development. Mesenchymal stem cells (MSC) were offered up as a potential COVID-19 therapy because of their immune modulating characteristics and successful use in other acute respiratory diseases. Two *CT* author groups gave proof of principle when hospitalized COVID-19 patients were infused with MSC after no other interventions seemed to work. MSC treatment reduced disease severity and shortened hospitalization stays. Lastly, *CT* authors speculated why we are still in the midst of a pandemic and the consequences of disillusioned comfort as we face new emerging variants that may undermine all we have accomplished thus far.

Keywords

cellular therapy, mesenchymal stem cells, cytokines, SARS-CoV2

Introduction

Over the past 18 months or so, as COVID-19 spread, *Cell Transplantation (CT)* published 13 articles on the disease and the virus which causes it, SARS-CoV2. These papers were written to inform us which people, tissues, or cells were susceptible to infection[1–4], how the micro-immune environment could spin itself into a cytokine storm[5], and to offer expert suggestions about how the disease could be treated[7–14]. What all of these articles had in common was a sense of hope- that while SARS-CoV2 runs rampant for now, we might soon have it under control. At the time many of these papers were written, the global death toll was just passing 500,000 deaths; it seemed unlikely that little more than a year later (August 2021) the number of deaths in the USA alone would surpass 500,000 with a worldwide death toll over four million.

COVID-19 Hypotheses

COVID-19 disease has a variety of onset symptoms—fever, cough, anosmia, diarrhea, headache, and so on—which can develop into different levels of severity. A small portion of the population can become infected but show no symptoms while others show severe symptoms which can quickly degrade into acute respiratory distress syndrome (ARDS)[6]. Among those with severe disease, the outcome can vary from complete recovery to death, with many in between becoming "long-haulers," experiencing lingering health problems even after they recovered from the acute phase of the illness.

To better understand why individuals react differently to the SARS-CoV2 virus, Ravaioli and colleagues explored

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gene variants in the angiotensin-converting enzyme 2 (ACE2) and the transmembrane serine protease 2 (TMPRSS2), the transmembrane proteins necessary for the SARS-CoV2 to infect cells[3]. The group harvested data from the Tissue Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) portal. One variant in particular—S19P—was identified in a region associated with viral docking on ACE2. Although it had a low frequency, it was exclusively found in samples taken from those of African descent. In their article, Ravaioli et al. speculated that these variants could influence the ability for SARS-CoV2 to infect cells. A recent article by Barton *et al.*[15] seems to confirm their speculations. ACE2 variants, S19P and K26 R, both appear to increase SARS-CoV2 binding according to *in vitro* data.

From the same group, Bravaccini *et al*. looked at the androgen receptor and its role in SARS-CoV2 infections[1]. Their idea stemmed from previous work (pre-COVID-19) revealing the connection between TMPRSS2 and the androgen receptor and data showing the immunomodulatory effects of sex hormones[16,17]. Bravaccini and colleagues speculated that hormone blockers, like tamoxifen which inhibits androgen receptor activity, could be used in the treatment of COVID-19 patients. This idea has since been supported by reports from others which found that prostate cancer patients on androgen-deprivation therapy have a decreased likelihood of developing severe COVID-19[18]. Clinical trials exploring the use of hormone therapies are currently underway[19–23]. In one completed trial by Applied Biology[23], proxalutamide treatment in moderately ill, non-hospitalized men decreased symptom severity and decreased the likelihood of hospitalization.

Several *CT* articles this past year proposed the use of mesenchymal stem cells (MSC) to treat COVID-19 infected patients[8,9,12–14]. MSC have several advantages as an immunomodulating therapy. Data suggests they are capable of the following:

- Inhibiting T-lymphocyte and macrophage activation
- Inhibiting the secretion of pro-inflammatory cytokines, particularly IL6 and TNFα
- Inducing the release of growth factors that support lung tissue repair (i.e., hepatocyte growth factor, keratinocyte growth factor (KGF), VEGF)
- Promoting the release of anti-inflammatory cytokines, like IL10

In specific reference to COVID-19, MSC are ACE2 and TMPPRS negative and are thus unlikely to become infected. Furthermore, IV infusions of MSC cause the bulk of them to become trapped in the lungs, the primary site of SARS-CoV2 infection. Thus MSC could modulate the innate immune response, muting or preventing the toxic cytokine storm induced by SARS-CoV2, and support lung tissue repair[5].

The speculation around the usefulness of MSC in treating COVID-19 may already be supported. MSC have been beneficial in animal models of ARDS and were used to treat patients suffering from influenza A (H7N9 infections)[9,12,14]. In critically ill COVID-19 patients who have failed to respond to all other treatments, MSC have been used almost as a last-ditch effort[7,11,12]. Fortunately, MSC infusions had a relatively quick and lasting effect, by decreasing pro-inflammatory cytokines (TNFα) and inflammatory markers (i.e., CRP), and increasing anti-inflammatory cytokines (IL10) and growth factors (KGF). In their *CT* article, Adas *et al.*[7] reported that a MSC treated patient group had a shorter ICU length of stay and fewer deaths. The Senegaglia *et al*.[11] case report told the story of an intubated COVID-19 patient that was extubated six days after the first of three MSC infusions, discharged from the ICU 4 days later, and left the hospital shortly after that.

COVID-19 Today

In a *CT* article by Hu et al., they described three individuals that were positive for COVID-19 yet displayed no symptoms of illness[2]. They warn that these covert cases could lead to another outbreak and they stressed the importance of COVID-surveillance methods in addition to standard social distancing, good hygiene, and mask wearing. However, these covert cases are not likely the sole reason why the COVID-19 pandemic continues to rage. A *CT* editorial offers another, more disturbing reason why we are still fighting- disillusion comfort[8].

Disillusioned comfort is the misguided sense of security that some have regarding the dangerous nature of COVID-19 that allows them to continue "life as usual," ignoring recommendations on social distancing, masks, and hygiene[8]. This attitude held by some likely accounts for many of the COVID infections and deaths; but more disturbing, it seems certain that it has contributed to the emergence of new and more infectious variants of SARS-CoV2, notably the recently surging Delta variant[24].

For many the answers did not and will not come quickly enough but just as the Spanish flu pandemic taught us the importance of social distancing and good hygiene, what we learn about COVID-19 disease now will help us be ready for the next pandemic. For now, we commend the development of SARS-CoV2 vaccines.

Messenger RNA (mRNA) vaccines have been under development for years against such viral diseases as HIV, Zika, and influenza as well as against different types of cancers like melanoma, glioblastoma, prostate and breast cancer[25]. The rise of COVID-19 has certainly amplified the area of mRNA- and DNA-based vaccine research and application. Based on the past 18 months of studies, case reports, and commentaries published in *CT*, we hope to continue being a means for such advances in COVID-19.

Disclosure

The authors report no conflicts of interest in this article and acknowledge that the citations of the COVID-19 papers could influence metrics.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

This study was approved by our institutional review board.

Statement of Human and Animal Rights

This article does not contain any data derived from human or animal subjects.

Statement of Informed Consent

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